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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/103,846	06/24/1998	RICHARD P. WOYCHIK	CASE-03330	3529

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EXAMINER
WOITACH, JOSEPH T

ART UNIT	PAPER NUMBER
1632	26

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Please find below and/or attached an Office communication concerning this application or proceeding.

[redacted] [redacted] File

Office Action Summary	Application No. 09/103,846	Applicant(s) Woychik, R. et al.
	Examiner Joseph T. Woitach	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *Jul 17, 2002*

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8, 10-12, 14-22, 24-26, 28, 35-37, 39-46, and 48-50* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideratio

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, 10-12, 14-22, 24-26, 28, 35-37, 39-46, and 48-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examine

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some* c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 16, 2002, paper number 24, has been entered.

DETAILED ACTION

This is an original application was filed June 24, 1998.

Applicants' amendment filed July 16, 2002, paper number 25, has been received and entered. Claims 38 and 47 have been canceled. Claims 37 and 46 have been amended. Claims 1-8, 10-12, 14-22, 24-26, 28, 35-37, 39-46 and 48-50 are pending and currently under examination.

Specification

The objection to the disclosure because the specification contains several references to a URL (for example: page 22; line 18) is maintained.

Applicants argue that the URLs and the incorporation by reference of the material contained at these sites is not directed to "essential material", and argue that the objection is

unwarranted citing MPEP 608.01(p) in support of their arguments. See Applicants' amendment, pages 6-7. Applicants' arguments have been fully considered, but not found persuasive.

MPEP 608.01(p) states "Nonessential subject matter may be incorporated by reference to (1) patents or applications published by the United States or foreign countries or regional patent offices, (2) prior filed, commonly owned U.S. applications, or (3) non-patent publications however, hyperlinks and/or other forms of browser executable code cannot be incorporated by reference." (emphasis added). Further, "Nonessential subject matter is subject matter referred to for purposes of indicating the background of the invention or illustrating the state of the art." See MPEP § 608.01. Applicants arguments are not found persuasive because the MPEP clearly indicates that neither "essential material" nor non-essential subject matter can be incorporated by use of hyperlinks. Therefore, the attempt to incorporate subject matter into the patent application by reference to a hyperlink an/or other forms of browser-executable code is considered to be an improper incorporation by reference, and the objection is maintained.

Claim Objections

Claims 42 and 45 objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn.

Applicants argue that the claims 42 and 45 do limit claim 37 because each of the method steps specifically recited in claims 42 and 45 are different and further limit the possible scope of all possible method steps or uses of the product produced in claim 37. See Applicants'

amendment, pages 7-8. Applicants' arguments have been fully considered and have been found persuasive. Specifically, while the steps in claims 42 and 45 are drawn to additional method steps, given the open language of claim 37, they do further limit the claims by excluding any other possible method step.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8, 10-12, 14-22, 24-26, 28, 35-37, 39-46 and 48-50

are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 15, 35 and 36 are vague and incomplete. The preamble of the claim recites that the method is drawn to producing a modification in a gene of interest in a cell wherein the target cell is an embryonic cell selected from either (1) a fertilized egg or (2) a 2-cell embryo, and the final step results in isolating said embryonic cells having a modified gene of interest. The antecedent basis for the "said embryonic cells" is in step (a)(i), however it is unclear how one isolates an embryonic cell claim, being either a fertilized egg or a 2-cell embryo given in the limitations in claim, without either allowing the cell to proliferate further or destroying the cell itself. There is no specific detection step or method of isolation recited, and in view of the teachings in the present specification it is unclear because how one accomplishes treating a cell

of interest and isolating the same cell with a specific genetic alteration of interest. Dependent claims are included in the basis of the rejection because they fail to further clarify how a fertilized egg cell or 2-cell embryo with the genetic alteration of interest would be isolated as required in the final step. For example, given the teachings in the present specification, it is unclear how on would amplify (claim 4), sequence (claim 5) or use chemical cleavage (claim 45) with the gene of interest without destroying the cell, in particular, without first identifying the cell with the alteration of interest. Additionally, none of the chemicals recited (claim 14) specifically target any particular gene wherein one could generate a specific alteration in a gene of interest.

Claims 3, 17 and 42 are confusing because the independent claim from which it depends is a method of producing a modification in a gene of interest in a cell, not a method of generating a non-human animal or mouse. Rewriting the claim as an independent claim would obviate the basis of the rejection.

Claim 37 the recitation of "the genes" lacks proper antecedent basis because two types of genes are previously recited in the claim, a gene of interest and every gene in the genome, and it is unclear to which "the genes" refers. It is unclear if 70% of the time the gene of interest has an alteration or if 70% of the genes in the genome are altered. Further, the claim is vague and unclear to whether a mutation is present in every gene in a single cell or if each cell in the culture has at least one mutation wherein the population of cells represents all the potential gene alterations. Additionally, the claim is confusing in the recitation of "at least 70% of the genes in

said mouse" in step (b)(ii) because step (b)(i) requires that a "modification in substantially every gene in said mouse embryonic stem cells is produced". The claim is indefinite because these two limitation are in conflict and it is unclear if a mutation in every gene is required or only 70% of the genes. The support for the limitation at page 14 in the present specification is noted, where "substantially every cell" is described as a statistical probability, however "every gene" is inconsistent with less than 100%. More clearly setting forth the metes and bounds encompassed by the treatment set forth in the claim would obviate the basis of the rejection. Dependent claims are included in the basis of the rejection because they fail to further clarify the basis of the rejection. For example, claims 39 and 40 recite alternative percent of modifications without defining to what the percentages refer.

Claim 41 is confusing in the embodiment and recitation using "200 to 600 embryonic stem cells" because claim 37 requires that substantially every gene contain a modification, however there are proposed to be from 10,000 to 100,000 possible genes in a given genome, and thus, it would require 10-100,000 cells having at least one alteration in a gene of interest.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who

has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-8, 10-12, 14-22, 24-26, 28, 35-37, 39, 40, 42, 43, 46, 48 and 49 rejected under 35 U.S.C. 102(e) as being anticipated by Schafer *et al.* is withdrawn.

Applicants argue that Schafer *et al.* does not anticipate the instant claims because they do teach the cell types specifically recited in the claim, namely fertilized egg cells and cells of 2-cell embryos. See Applicants' amendment, pages 9-10. Applicants' arguments have been fully considered and found persuasive.

Specifically, Schafer *et al.* teach that mutagenesis can be performed in a whole organism and on a wide range of cell types (column 6), but do not specifically recite to use fertilized egg cells and cells of 2-cell embryos. Therefore, because Schafer *et al.* does not teach each limitation of the of the claim, the claim is not anticipated by the teachings of Schafer *et al.*

Claims 37, 39, 40, 43, 45, 46, 47 and 49 rejected under 35 U.S.C. 102(e) as being anticipated by Goodfellow *et al.* is withdrawn.

Applicants point out that Goodfellow *et al.* do not specifically recite nor teach conditions wherein "at least one modification is produced in substantially every gene in said mouse embryonic stem cells" nor "that at least one modification in at least about 70% of the genes" is produced. Applicants summarize the teaching of Goodfellow *et al.* and argue that the specific

limitation in the pending claims are not taught in Goodfellow *et al*. See Applicants' amendment, pages 10-12. Applicants' arguments have been fully considered and found persuasive.

Specifically, Goodfellow *et al*. teach conditions wherein the treatment results in a mutation rate in the gene of interest, but do not specifically teach conditions for the complete composition of embryonic cells treated. Therefore, because Goodfellow *et al*. does not specifically teach each limitation recited in the claim, the claim is not anticipated by the teachings of Goodfellow *et al*.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8, 10-12, 14-22, 24-26, 28, 35-37, 39, 40, 42, 43, 46, 48 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schafer *et al*.

Previously, claims 1-8, 10-12, 14-22, 24-26, 28, 35-37, 39, 40, 42, 43, 46, 48 and 49 were rejected as being anticipated by Schafer *et al.*, however as noted above, Schafer *et al.* does not specifically recite the limitation to use fertilized egg cells or cells of 2-cell embryos. Schafer *et al.* teaches that one can use the described methods with any cell and provides specific, but non-limiting examples, for the use of "the germline cells of an organism, such as sperm stem cells or ova", "embryonic stem (ES) cells of an organism" or the cells of "an organism" (column 6; lines 58-65). Clearly, Schafer *et al.* teaches that any cell can be used, and given the specific examples, the types of cells contemplated cover any cell from the germline to the intact organism. Between fertilization of the ova with a sperm and the resulting organism, fertilized egg cells and the 2 cell embryo would be obvious variants encompassed by the teachings of Schafer *et al.* The fertilized egg cells and the 2 cell embryo are part of the continuum of any kind of cell contemplated by Schafer *et al.*, and would be an obvious limitation given the breadth to use any cell and the specific example provided by Schafer *et al.* Upon review of the present disclosure there is no unexpected results gained from using a fertilized egg cells or a 2 cell embryo, and thus, given the teaching of Schafer *et al.* there would have been a reasonable expectation of success to use a fertilized egg cells or a 2 cell embryo in the methods disclosed.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Claims 37-40, 43, 45-47 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodfellow *et al.*

Previously claim 37-40, 43, 45-47 and 49 were rejected under 35 USC 102(e) as being anticipated by Goodfellow *et al.*, however as noted above, Goodfellow *et al.* does not specifically recite the limitation to mutate every gene within the genome of an organism or teach the specific limitation of 70% to 95% which represents the statistical probability of altering every gene in the genome (or alternatively the a particular gene of interest) to obtain an set of genetic alterations in a gene of interest. It is noted that Goodfellow *et al.* teach that the mutagenizing step should be done where about 1 mutation occurs in every 10,000-1,000 genes with the average in frequency of 1/500 and preferably 1/1000-1/10,000 (column 4; lines 18-20 and lines 31-34). Additionally, Goodfellow *et al.* indicate that the art teaches that there may be 50-100,000 unique genes in development and 30,000 unique ESTs representing different genes. It is important to note that the general teachings of Goodfellow *et al.* are directed to the **rate** of mutagenesis **per cell** for a specific gene of interest. As noted above in the rejection made under 35 UCS 112, second paragraph, the limitation of "at least 70% of the genes" is unclear, however a fair interpretation is that 70% of the cells in the culture have a random genetic alteration. The process of mutagenesis taught in Goodfellow *et al.* and the present specification are the same, requiring the use of various known mutagens and practicing the method step of mutagenesis in light of the known and inherent properties of any specific mutagen. Further, the mutagenesis step in both cases is a random process each depending on the statistical probability of introducing a mutation into the genome, and based on the size of the genome the statistical probability that the alteration is made in the gene of interest. Finally, it is important to note that each of the methods taught and

instantly claimed are directed to an undefined "gene of interest", and that any and all genes are contemplated by Goodfellow *et al.* and the present disclosure. By itself, the fact that any gene may be a gene of interest, using the method described by Goodfellow *et al.* would make obvious making mutations in <u>every</u> gene in the genome because any and all genes are encompassed as gene of interest.

With respect to Applicants' arguments regarding the previous rejection of record, Applicants argue that the ranges taught by Goodfellow *et al.* do not overlap or anticipate those specifically recited. See Applicants' amendment, pages 10-12. Applicants' arguments have been fully considered but not found persuasive because the arguments are based on comparison of rates in a gene of interest as taught by Goodfellow *et al.* and absolute percent number of alterations in a genome as recited in the claims. First, it is important to note that the teaching of Goodfellow *et al.* make obvious targeting any gene of interest. Second, the methodology for mutagenesis taught in the instant specification and that taught by Goodfellow *et al.* are the same. It appears that Applicants' are arguing that the present method is distinguished from that of Goodfellow *et al.* because the present method first alters every gene then from every altered gene the altered gene of interest is selected whereas the teaching of Goodfellow *et al.* focus their discussion primarily on conditions for the gene of interest, not every gene within the genome. It is true Goodfellow *et al.* teach a rate of mutagenesis which is preferably 1/500 to 1/10,000 in the gene of interest, however because the process of mutagenesis is a random process encompassed in this rate is the fact that at least the remaining 499 to 9,999 other possible alterations are in

other genes of the genome. Applicants' point to the teaching that "1 mutation occurs in every 10,000-1,000 genes" (column 4, lines 17-19) and argue that this rate is much less than that instantly claimed or taught in the present disclosure, however the teaching in context is describing the number of mutations in an "organism" (see Applicants' amendment page 11 and column 4; line 19). Given that 50-100,000 genes are proposed to exist in a given genome, a single organism could contain at least 5 to 100 different gene alterations. If the animal was produced using embryonic stem cells which were mutagenized under the conditions taught in Goodfellow *et al.* for a gene of interest, every cell in a given culture would have contained at least one alteration in any other given gene. In the description of the invention Goodfellow *et al.* state that an "advantage of the methods of the invention is that a typical screen of 10,000 organisms is expected to identify 5-15 independent and different protein altering mutations for ***each*** gene tested." (emphasis added column 9; lines 44-47). Clearly Goodfellow *et al.* contemplated altering any gene as a gene of interest, and in light of the above recitation of the conditions taught in the patent resulting in 5-15 alterations in any gene tested, every gene must have contained a modification when practicing the methods of Goodfellow *et al.* Further, Goodfellow *et al.* teach that practicing the methods would result in organisms which would represent 'an "allelic series" of mutations in a particular gene' (column 9; lines 51-53). Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made that the conditions of mutagenesis taught by Goodfellow *et al.* would have resulted in introducing a modification in every gene. One having ordinary skill in the

art would have been motivated to practice the methods of Goodfellow *et al.* because the methods would provide the ability to study an allelic series of gene alterations and may give insight into disease states in humans (column 9; lines 51-56). There would have been a reasonable expectation of success given the specific teaching and guidance of Goodfellow *et al.* and in light of the working examples demonstrating the ability of the methods to generate a series of mutations in several genes of interest.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Claims 1-8, 10-12, 14-22, 24-26, 28, 35-40 and 42-50 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Schafer *et al.*, Goodfellow *et al.* in view of either Kohler *et al.* (IDS reference JNCI, 1993) or Guay-Woodford *et al.* (IDS reference J. Int. Soc. Neph., 1996).

Applicants argue that none of the requirements for making a *prima facie* case have been established and thus, the rejection is improper. Specifically, Applicants argue that the specific cell types, namely "fertilized egg cells and cells of 2-cell embryos", the limitation of "at least one modification is produced in substantially every gene in said mouse embryonic stem cells" and a method of detection comprising "fluorescent chemical cleavage" are not disclosed. Applicants argue that there is no motivation to combine these references and are irrelevant to claims 1-8, 10-12, 14-22, 24-26, 28, 35-40, 42, 42, and 45-49 because these claims do not require p53 or PKD, and with respect to claims 37-40, 42, 43 and 45 they do not meet the limitation

required by the claims. Finally, Applicants argue that the case for a reasonable expectation of success has not been made because the extrapolation between the working examples of Schaffer and Goodfellow for mutagenesis of a gene of interest and the teachings of other genes in other cell types. See Applicants' amendment, pages 13-16. Applicants arguments have been fully considered but not found persuasive.

As explained above in detail, the teaching of Schafer *et al.* and Goodfellow *et al.* make obvious claims 1-8, 10-12, 14-22, 24-26, 28, 35-40, 42, 43, 45- 48 and 49. Briefly, both Schafer *et al.* and Goodfellow *et* al. teach methods of chemical mutagenesis of embryonic cells for identifying a mutation in a gene of interest. Each provide a general overview and detailed guidance on the chemical properties of known mutagens and methods of using said mutagens for generating a mutation in a gene of interest. The general intended use of the methods is for the characterization of a gene of interest, and Goodfellow *et al.* specifically teaches that the disclosed methods of genetic modifications can be used to generate animal models of human diseases (column 8; lines 30-61), and both Schafer *et al.* and Goodfellow *et al.* teach that the methods can be used for any gene of interest and the necessary methodology to affect the methods. It is noted that Goodfellow *et al.* does not specifically recite the use of a fluorescent chemical cleavage method, however it generally taught that any method conventional in the art can be used and multiple methods of detecting a resulting mutation are specifically taught including a chemical cleavage method. In the instant case the limitation of using a fluorescent probe as a variation of a chemical cleavage method would be obvious over the teachings of Goodfellow *et al.* In

addition, as previously noted, neither specifically teach the gene recited in claims 44 and 50. The teaching of Kohler *et al.* and Guay-Woodford *et al.* are relied on only to demonstrate that p53 and PKD would be recognized as two genes of interest. The process of mutagenesis is random process and mutations in both p53 and PKD would be generated practicing the methodology set forth in Schafer *et al.* and Goodfellow *et al.* Further, the teaching and study of a spectrum of mutations in p53 and modifications of PKD as set forth in Kohler *et al.* and Guay-Woodford *et al.* clearly indicate that these genes represent genes of interest. Applicants arguments regarding an extrapolation between different cell types is confusing, and not found persuasive because the cells taught in Kohler *et al.* and Guay-Woodford *et al.* are not relied upon, rather it is the characterization and implications of the mutations in their respective disease conditions described by each Kohler *et al.* and Guay-Woodford *et al.* indicating that p53 and PKD are genes of interest with respect to the genetic linkage to their respective diseases. It is noted, that the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. *In re Nilssen*, 7 USPQ2d 1500 (Fed. Cir. 1988). Further, it is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. *In re Burkel*, 201 USPQ 67 (CCPA 1979). Furthermore, in the determination of obviousness, the state of the art as well as the level of skill of those in the art

are important factors to be considered. The teaching of the cited references must be viewed in light of these factors, and in the instant case the teaching of Kohler *et al.* and Guay-Woodford *et al.* clearly demonstrate that p53 and PKD genes were genes of interest and a subject of active research. Further, each Kohler *et al.* and Guay-Woodford *et al.* discuss the need to further analyze the effects and consequences these mutations and other mutations within these genes. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the methods described by Schafer *et al.* and Goodfellow *et al.* for the genes of interest specifically taught in Kohler *et al.* or Guay-Woodford *et al.* One having ordinary skill in the art would have been motivated to pick p53 and PKD genes as genes of interest because of their implicated roles in human diseases and because of the need for further characterization in these diseases. There would have been a reasonable expectation of success to target p53 and PKD as genes of interest given the successful results of Schafer *et al.* and Goodfellow *et al.* for several other genes of interest, and the teachings of both Kohler *et al.* and Guay-Woodford *et al.* that specific mutations can be made and already exist and result in detectable phenotypic changes. Note that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See *In re O'Farrell*, 7 USPQ2d 1673 (CAFC 1988). In the instant case, both Kohler *et al.* and Guay-Woodford *et al.* have demonstrated that mutations in the p53 and PKD genes are obtainable and provide evidence that cells containing these mutations exist and are a subject of active research.

Thus, the claimed invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claim is allowed.

As noted previously, claim 41 is free of the art of record because the art fails to teach that as little as 200-600 ES cells could successfully be used in the recited methods. The closest teaching to this low range of cells as a starting material is by Schafer *et al.* who suggest that as few as 1000 organisms (i.e cells) could be used to obtain a single mutant copy of a gene (column 6; lines 45-54). In addition, Schafer *et al.* do teach as little as 300 mice can be used (Example 1: column 14; lines 58-67), however in this example the spermatogonia are the target cells, and thus, represent many more cells as starting material than 300 cells, and therefore would be outside the range of 200-600 cells.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached at (703)305-4081.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist Pauline Farrier whose telephone number is (703)305-3550.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630